PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Acupuncture treatment for ischemic stroke in young adults: protocol for a randomized, sham-controlled clinical trial
AUTHORS	Chen, Lifang; Fang, Jianqiao; Jin, Xiaoming; Keeler, Crystal; Gao, Hong; Fang, Zhen; Chen, Qin

VERSION 1 - REVIEW

REVIEWER	Dr Val Hopwood FCSP Clinical Editor Acupuncture in Physiotherapy UK
REVIEW RETURNED	20-Oct-2015

GENERAL COMMENTS	A timely and interesting protocol. Good to see such lengthy follow-ups. Why are BI and FMA only optional at 10 and 30 years? Any later illness or damage not related to the stroke could be discounted. I know this is an old criticism of acupuncture studies but was a third 'no acupuncture' group considered? The sham group receives a complex and lengthy intervention which in Western hospitals would be a) convincing to the patient and b)would appear to the critics to have effects very close to the real treatment. Are the researchers convinced that this sham acupuncture would be genuinely inert? I agree that the subjects must be acupuncture naive. Knowing the difficulties in this field I support the acceptance of this protocol but I would like to see some discussions of these issues in the limitations.

REVIEWER	Sae Uchida Department of Autonomic Neuroscience, Tokyo Metropolitan Institute of Gerontology
REVIEW RETURNED	21-Oct-2015

GENERAL COMMENTS	In this clinical trial, the authors focus on young ischemic stroke and aim to examine the effects of acupuncture treatment. This trial is worth to examine. Followings are the comments to the authors that should be consider. Major comments 1. Study Design Natural recovery after stroke may be greater in young adult than in older adult. I recommend to add the group of “only conventional rehabilitation treatment”.

	2. Outcome Measures-primary outcomes I recommend to add “Cognitive tests” as outcome measures. Because there are already many studies measuring ADL, motor function, and QOL. 3. Outcome Measures-secondary outcomes “Body temperature” and “oxygen saturation” should be added as outcome measures, since these parameters are fundamental assessment for physiological state.

REVIEWER	Byung-Cheul Shin Pusan National University, South Korea
REVIEW RETURNED	01-Nov-2015

GENERAL COMMENTS	In this manuscript, the authors planned a randomized, sham-controlled, clinical trial which tested the efficacy and safety of acupuncture for young adults stroke to determine whether acupuncture treatment would be effective in improving the activities of daily living (ADL), motor function, and quality of life (QOL) in patients of young ischemic stroke, and in preventing stroke recurrence by controlling blood pressure, lipids and body weight. This study protocol seemed well designed and was following recommended current reporting guideline of SPIRIT or ethical clinical trial procedure with rigorous manner. Therefore I would like to give minor comments on it for helping the improvement of quality with balanced view points. 1. How about adding the word ‘ischemic’ in your title for clear understanding of population studied. 2. Please add ‘sham-controlled’ in key words for better search. 3. Please check your manuscript following the reporting guideline of CONSORT 25 items [1] and STRICTA recommendation for acupuncture study [2]. Even though your protocol follows study protocol reporting guideline of SPIRIT, when you report your results, two reporting guideline will be helpful for your future submission of your final results. [1] http://www.consort-statement.org/ [2] http://www.equator-network.org/reporting-guidelines/consort-stricta/ 4. There is scare information about assessor blinding and allocation concealment. 5. Please add the information of usual care for stroke (drug, rehabilitation, etc). If same usual care was used for two groups in parallel with acupuncture or sham-acupuncture, please report it for comparing no difference between two groups. Additionally my suggestion is you should input the data of stroke severity for adjusting the data of primary/secondary outcomes or for comparing no difference between two groups. 6. Please check abbreviations with consistency in main text. Define it at the first appearance, then use it after the definition. E.g.) EDC in page 11, traditional Chinese medicine in page 12, activities of daily living in page 13, quality of life in page 14, etc.

	7. Please check your referencing method in the section of reference. 50-58. in ref. 13 -> 50-8. 8. Please add abbreviations in Table 1 at the bottom of table. Eg. FMA, WHOQOL-BREF

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Dr Val Hopwood FCSP
Institution and Country: Clinical Editor Acupuncture in Physiotherapy, UK.

Please leave your comments for the authors below

A timely and interesting protocol.
Good to see such lengthy follow-ups.
1.Why are BI and FMA only optional at 10 and 30 years? Any later illness or damage not related to the stroke could be discounted.
Response: BI used as the primary outcome in this trial, is a easy tool to estimate ADL even by telephone contact. So we changed BI to required assessment at 10-year and 30-year follow-ups. However, FMA is a very professional and time-consuming tool to assess motor function, it is inconvenient to be applied in follow-ups for all participants. After all, the main purpose of the long-term follow-up is to observe the mortality, recurrence rate of stroke, ADL, and QOL (pg.11).
2.I know this is an old criticism of acupuncture studies but was a third 'no acupuncture' group considered?
The sham group receives a complex and lengthy intervention which in Western hospitals would be a) convincing to the patient and b) would appear to the critics to have effects very close to the real treatment.
Are the researchers convinced that this sham acupuncture would be genuinely inert?
I agree that the subjects must be acupuncture naive.
Knowing the difficulties in this field I support the acceptance of this protocol but I would like to see some discussions of these issues in the limitations.
Response:
Thanks for your wonderful suggestion.
Including a third, “no acupuncture” group will improve the control design in our acupuncture trial. The possibility of a placebo effect, particularly for those who believe in traditional medicine, should not be dismissed; however, sham acupuncture interventions might, on average, be associated with larger effects than pharmacological and other physical placebos (Linde K, Niemann K, Meissner K. Are sham acupuncture interventions more effective than (other) placebos? A re-analysis of data from the Cochrane review on placebo effects. Forsch Komplementmed 2010;5:259-64). Some of the sham acupuncture methods may also produce physiological activity (CARNEIRO M, KAWAKITA K. Re-analysis of acupuncture trials with sham interventions based on data from the Cochrane Review. Japanese Acupuncture and Moxibustion 2015;1:1-11). The nature of the placebo effect that is associated with sham acupuncture is an entire field of study unto itself. We consulted several Chinese acupuncture experts, many of whom believed that the effect of acupuncture for stroke is closely related with the stimulation of acupoints and meridians and "De Qi," which is in accordance with the ancient TCM theory that states, “no De Qi, no effects.” These experts believe that sham-acupuncture that is designed as “superficial needle insertion and minimal stimulation at non-acupoint and non-meridian areas” in this trial could produce a placebo effect, but with no additional efficacy (or that a reduced influence by the sham acupuncture could be ignored when compared with real acupuncture).

Nevertheless, in an acupuncture analgesia clinical trial, a sham-acupuncture (of any type) could produce additional influence beyond that of a placebo. In our experience, sham acupuncture may produce different effects in different diseases. This may be because of the different mechanisms of acupuncture treatment for different diseases. For example, stroke is a major and complex disease while acupuncture treatment for stroke should focus on regulating the whole body and under the guideline of TCM theory. For painful syndromes, acupuncture treatment is much simpler to perform and easier to produce effects even if we do not select acupoints and meridians and only use local points. In this respect, the influence of sham-acupuncture for pain may be greater than that of stroke. Taking into account that sham-acupuncture may have little effect on the treatment of stroke, but could eliminate the placebo effect, we reasoned that sham-acupuncture is an ideal control setting in this trial so long as it is conducted well. This conclusion is based upon our clinical practice and requires further study. We will consider the nature of sham acupuncture in future studies to maximize the avoidance of this limitation. (pg.16,17).

Reviewer: 2
Reviewer Name: Sae Uchida
Institution and Country: Department of Autonomic Neuroscience, Tokyo Metropolitan Institute of Gerontology, Japan.

Please leave your comments for the authors below

In this clinical trial, the authors focus on young ischemic stroke and aim to examine the effects of acupuncture treatment. This trial is worth to examine. Followings are the comments to the authors that should be consider.

Major comments
1. Study Design
Natural recovery after stroke may be greater in young adult than in older adult.
I recommend to add the group of “only conventional rehabilitation treatment”.
Response: All participants of both groups will get natural recovery after stroke; this issue will be comparable in randomized groups.
Thanks for your wonderful suggestion. Including a third, “no acupuncture” group will improve the control design in our acupuncture trial. The possibility of a placebo effect, particularly for those who believe in traditional medicine, should not be dismissed; however, sham acupuncture interventions might, on average, be associated with larger effects than pharmacological and other physical placebos (Linde K, Niemann K, Meissner K. Are sham acupuncture interventions more effective than (other) placebos? A re-analysis of data from the Cochrane review on placebo effects. Forsch Komplementmed 2010;5:259-64). Some of the sham acupuncture methods may also produce physiological activity (CARNEIRO M, KAWAKITA K. Re-analysis of acupuncture trials with sham interventions based on data from the Cochrane Review. Japanese Acupuncture and Moxibustion 2015;1:1-11). The nature of the placebo effect that is associated with sham acupuncture is an entire field of study unto itself. We consulted several Chinese acupuncture experts, many of whom believed that the effect of acupuncture for stroke is closely related with the stimulation of acupoints and meridians and "De Qi," which is in accordance with the ancient TCM theory that states, “no De Qi, no effects.” These experts believe that sham-acupuncture that is designed as “superficial needle insertion and minimal stimulation at non-acupoint and non-meridian areas” in this trial could produce a

placebo effect, but with no additional efficacy (or that a reduced influence by the sham acupuncture could be ignored when compared with real acupuncture). Nevertheless, in an acupuncture analgesia clinical trial, a sham-acupuncture (of any type) could produce additional influence beyond that of a placebo. In our experience, sham acupuncture may produce different effects in different diseases. This may be because of the different mechanisms of acupuncture treatment for different diseases. For example, stroke is a major and complex disease while acupuncture treatment for stroke should focus on regulating the whole body and under the guideline of TCM theory. For painful syndromes, acupuncture treatment is much simpler to perform and easier to produce effects even if we do not select acupoints and meridians and only use local points. In this respect, the influence of sham-acupuncture for pain may be greater than that of stroke. Taking into account that sham-acupuncture may have little effect on the treatment of stroke, but could eliminate the placebo effect, we reasoned that sham-acupuncture is an ideal control setting in this trial so long as it is conducted well. This conclusion is based upon our clinical practice and requires further study. We will consider the nature of sham acupuncture in future studies to maximize the avoidance of this limitation. (pg.16,17).
2. Outcome Measures-primary outcomes
I recommend to add “Cognitive tests” as outcome measures.
Because there are already many studies measuring ADL, motor function, and QOL.
Response: Most of the stroke clinical trials focus on ADL, motor function or QOL as the primary outcome measurements. To the best of our knowledge, this trial will be the first study concerning on acupuncture treating and preventing specifically for YOUNG stroke. The main aim of this trial is to demonstrate whether acupuncture compared to a sham control group will be effective in improving outcomes after stroke in young adults, as well as improving risk factors associated with recurrent stroke. Because the ultimate goal of stroke is always focused on the ADL of patients toward greater independence, we preferred to use BI as the primary outcome in this trial.
3. Outcome Measures-secondary outcomes
“Body temperature” and “oxygen saturation” should be added as outcome measures, since these parameters are fundamental assessment for physiological state.
Response: We recorded the basic physiological parameters (eg: body temperature, breath, pulse, heart rate, ect.) of all subjects in case history. However, we only selected some of them related with acupuncture treatment as outcome measures.

Reviewer: 3
Reviewer Name: Byung-Cheul Shin
Institution and Country: Pusan National University, South Korea

Please leave your comments for the authors below

In this manuscript, the authors planned a randomized, sham-controlled, clinical trial which tested the efficacy and safety of acupuncture for young adults stroke to determine whether acupuncture treatment would be effective in improving the activities of daily living (ADL), motor function, and quality of life (QOL) in patients of young ischemic stroke, and in preventing stroke recurrence by controlling blood pressure, lipids and body weight.
This study protocol seemed well designed and was following recommended current reporting guideline of SPIRIT or ethical clinical trial procedure with rigorous manner. Therefore I would like to give minor comments on it for helping the improvement of quality with balanced view points.

1. How about adding the word ‘ischemic’ in your title for clear understanding of population studied.
Response: It’s necessary to add ‘ischemic’ in our title (pg.1). Thank you.
2. Please add ‘sham-controlled’ in key words for better search .
Response: We added sham-controlled in key words (pg.3).
3. Please check your manuscript following the reporting guideline of CONSORT 25 items [1] and

STRICTA recommendation for acupuncture study [2]. Even though your protocol follows study protocol reporting guideline of SPIRIT, when you report your results, two reporting guideline will be helpful for your future submission of your final results.
[1] http://www.consort-statement.org/
[2] http://www.equator-network.org/reporting-guidelines/consort-stricta/
Response: We check the STRICTA checklist, and added more information as recommended (pg.8, 9,10).
4. There is scare (scarce) information about assessor blinding and allocation concealment.
Response: All of the rehabilitation therapists, outcome assessors, and data analysts will be blinded to group assignments (pg.8). The generated list of random numbers will be placed into sequentially numbered, opaque, sealed envelopes. Consecutive patients will be randomly assigned to acupuncture group (AG) or sham acupuncture group (SG) in a 1:1 ratio according to the information they got from the envelopes (pg.8).
5. Please add the information of usual care for stroke (drug, rehabilitation, etc). If same usual care was used for two groups in parallel with acupuncture or sham-acupuncture, please report it for comparing no difference between two groups. Additionally my suggestion is you should input the data of stroke severity for adjusting the data of primary/secondary outcomes or for comparing no difference between two groups.
Response: Patients who will be included as eligible subjects should display clear consciousness and stable vital signs, with modified Rankin score (mRS) 2-4, and have no aphasia or cognitive dysfunction (pg.7).
Both groups will receive conventional stroke rehabilitation treatment and care during the whole 20-week study period. The program was designed according to Chinese stroke rehabilitation treatment guidelines and will be consistent across groups (Zhang T. Chinese stroke rehabilitation treatment guidelines 2011. Chin J Rehabil Theory Pract 2012;18:301-318), which included two-hours of physical therapy (PT) and one half-hour of occupational therapy (OT) for five days a week. Western medicine will be permitted for conventional symptomatic treatment (e.g., antihypertensive drugs and lipid-lowering drugs). Chinese herbal medicine and Chinese patent drugs will be prohibited during the trial (pg.9).
6. Please check abbreviations with consistency in main text. Define it at the first appearance, then use it after the definition.
E.g.) EDC in page 11, traditional Chinese medicine in page 12, activities of daily living in page 13, quality of life in page 14, etc.
Response: We checked all abbreviations with consistency in main text, defined ADL and QOL in the “Introduction” section (pg.6), defined EDC and TCM in page 12.
7. Please check your referencing method in the section of reference. 50-58. in ref. 13 -> 50-8.
Response: We have revised it. Thanks for your careful review.
8. Please add abbreviations in Table 1 at the bottom of table. Eg. FMA, WHOQOL-BREF.
Response: Abbreviations have been added at the bottom of table 1.

VERSION 2 – REVIEW

REVIEWER	Dr Val Hopwood FCSP Clinical Editor, Acupuncture in Physiotherapy. UK
REVIEW RETURNED	20-Nov-2015

GENERAL COMMENTS	This protocol has been much improved. The discussion section has been extended to deal with the issue of a 'no acupuncture treatment' and, whilst not solving the problem, has articulated the issues and explained some of the reasons for the current choice. The writing style has also been been clarified and the overall

	protocol descriptions are easy to follow and, possibly, replicate. It's very helpful to see the reviewed changes on the document. Thank you.

REVIEWER	Byung-Cheul Shin School of Korean Medicine, Pusan National Unviversity, South Korea
REVIEW RETURNED	07-Dec-2015

GENERAL COMMENTS	Thank you for your efforts, All issues were well answered.